REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim 40, 42-56 and 60 are requested to be cancelled. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

Claim 38 is currently being amended.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim remain under examination in the application, is presented, with an appropriate defined status identifier.

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. Upon entry of this Amendment, claims 38, 39, 41, and 57-59 will remain pending in the application.

II. September 27, 2004 Interview

Applicants thank the Examiner for the interview on September 27, 2004. The foregoing amendments and the following remarks incorporate suggestions made by the Examiner during the interview. Specifically, the claimed hPTH, as amended, is distinguished from the prior art on the basis of components present in the composition.

For example, as described in more detail below, synthetic PTH is distinguishable from the claimed hPTH as such synthetic PTH contains chemically modified protecting groups. Chemically modified protecting groups are undesirable, as such materials affect the biological activity of PTH and may cause the PTH preparation to be sufficiently different from the endogenously produced peptide to produce unwanted immunological responses in a patient receiving the hormone as a drug to treat disease.

III. Response to Issues Raised by Examiner in Outstanding Office Action

A. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 38, 39, 41 and 57-59 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that the claims lack enablement for the reasons of record set forth on pages 2-3 of the Office Action dated July 2, 2003, *i.e.*, it would allegedly not be predictable to the artisan which signal sequence would be effective in the method because the specification allegedly fails to provide guidance of any signal sequence other than MF□1 and MF□1 with an STE13 mutation.

In the December 31, 2003, Amendment, Applicants directed the Examiner's attention to a discussion of leader sequences that are useful for the claimed invention provided on page 23, line 30, through page 26, line 8, of the specification. In response, the Examiner asserts in the outstanding Office Action that because PTH and leader sequences were known at the time of the invention, "it is not understood why it would not have been obvious to the artisan at the time of the present invention to have added a known leader sequence to PTH for expression in *E. coli*." (outstanding Office Action, 12 lines from the bottom of page 2)

The standard the Examiner is applying in this rejection is "obvious to try." Applicants remind the Examiner that "'obvious to try' has long been held to not constitute obviousness." *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995). While it may have been "obvious to try" to utilize the known leader sequences for expression of PTH, one of skill in the art at the time the claimed invention was made *did not* have a reasonable expectation of success in expressing PTH utilizing such leader sequences.

Moreover, attached as Exhibit 1 is Høgset et al., *JBC*, *265*(13):7338-7344 (1990). Høgset et al. disclose expression of hPTH(1-84) in *E. coli* involving an expression plasmid where hPTH cDNA is fused to the signal sequence of *Staphylococcus aureus*-protein A. The expression yielded about 1 mg hPTH(1-84)/liter growth medium. *See e.g.*, page 7338, right panel, of Høgset et al. The hPTH(1-84) was purified using techniques well known to those of ordinary skill in the art at the time of the claimed invention (reverse-phase HPLC), as described on page 7340, right panel, of Høgset et al. Høgset et al. evidences that signal

sequences other than those exemplified in the specification are indeed effective in the claimed method.

Additionally, the Examiner asserts that "Applicants have only disclosed that a small number of signal sequences appear to be functional in the present invention (page 14, lines 15-35)." *See* Outstanding Office Action, 9 lines from the bottom of page 2. Applicants note that the discussion on page 14, lines 15-35, of the specification merely describes the use of the □-factor leader sequence, the leader sequence that is exemplified in the specification. Applicants remind the Examiner that Applicants are not limited by their enumerated examples.

As Applicants' claims are enabled, withdrawal of this ground for rejection is respectfully requested.

B. Issues Under Double Patenting

Claims 38, 39, 41 and 57-59 were *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over one or more claims of co-pending U.S. Application No. 08/340,664 ("the '664 application). Applicants respectfully request that the Examiner keep this issue in abeyance until either the present application or the '664 application is allowed.

C. Request for Information Under 37 C.F.R. § 1.105

The Examiner requires Applicants to provide all pertinent information regarding the source of the protein used as a standard. The Examiner notes that the specification at page 7 teaches the use of an hPTH (1-84) standard.

1. July 27, 2004 Declaration of Dr. Kaare Gauvik

Applicants attach as Exhibit 2 a Declaration of Dr. Kaare Gautvik pursuant to 37 C.F.R. § 1.132 dated August 27, 2004 (hereafter "Declaration 1"), which relates to the hPTH (1-84) standard referred to at page 7 of the specification. The hPTH (1-84) standard is synthetic hPTH (1-84) obtained from chemical supply companies, including Peptide Institute Protein Research Foundation, Penninsula Laboratories, Sigma, and Bachem.

The Declaration describes an SDS-PAGE gel in which 0.2 μg of hPTH (1-84) was loaded into various lanes. The hPTH (1-84) was obtained from: (a) Peptide Institute Protein Research Foundation (lane 2), Penninsula Laboratories (lane 3), Sigma (lane 4), or Bachem (lanes 5 and 6), or (b) produced according to the claimed invention (lanes 7, 8, and 9).

A picture of the SDS-PAGE gel is provided in Exhibit B of the attached Declaration.[1] The SDS-PAGE gel confirms that the synthetic hPTH (1-84) obtained from Peptide Institute Protein Research Foundation, Penninsula Laboratories, Sigma, and Bachem contains impurities as compared to the hPTH (1-84) produced according to the claimed invention.

While the synthetic hPTH (1-84) obtained from the various chemical companies contained impurities, the synthetic hPTH(1-84) preparations were useful as standards in confirming the identity of hPTH (1-84) produced according to the claimed invention.

2. October 19, 2004 Declaration of Dr. Kaare Gauvik

Applicants also attach as Exhibit 3 a Declaration of Dr. Kaare Gautvik pursuant to 37 C.F.R. § 1.132 dated October 19, 2004 (hereafter "Declaration 2"), which describes how the impurities discussed in Declaration 1 result in decreased PTH activity. Declaration 2 provides exemplary data for two of the synthetic PTH standards detailed in Declaration 1; from Sima and Bachem Fine Materials.

Paragraphs 5-8 of Declaration 2 describe a comparison of the purity of Applicants' hPTH(1-84) and Bachem's synthetic PTH via silver-stained SDS-PAGE analysis. The resulting gel shows that Applicants' recombinant hTPH (1-84) was assessed to be more than 95% pure. In contrast, the Bachem synthetic PTH preparation contained significant small molecular weight impurities, as demonstrated by the blurry bottom edge of the gel band (Exhibit B of Declaration 2).

Paragraphs 9-16 of Declaration 2 discuss data showing that the impurities present in Bachem's synthetic PTH resulted in significantly reduced biological activity as compared to

[1] Exhibit B is a reproduction of a photograph of the SDS-PAGE gel. Applicants showed the Examiner the original photograph of the gel at the September 27, 2004 interview and the Examiner made a photocopy of the gel for his files.

Applicants' claimed PTH(1-84). This reduced biological activity clearly indicates the non-authentic nature of the Bachem synthetic PTH preparation.

For example, the ability of the Bachem synthetic PTH preparation to bind to the receptor and induce cAMP production in cultured cells transfected with the rat PTH receptor was reduced by 40%, as compared to recombinant hPTH(1-84) from *E. coli* and yeast. *See* ¶ 10 of Declaration 2. Further, when tested *in vivo*, a similar reduced biological activity was observed for the Bachem synthetic PTH as compared to recombinant hPTH(1-84). This was determined by (a) measuring different PTHs' ability to increase blood calcium and (b) measuring changes in urinary cAMP, following injection of the two different PTH preparations to rats having their parathyroid hormone glands removed. *See* ¶¶ 11-16 of Declaration 2.

Paragraphs 17-19 of Declaration 2 describe the significant impurities present in Sigma's synthetic PTH as compared to Applicants' claimed hPTH(1-84). As discussed in Declaration 2, after two HPLC purifications steps, the recombinant hPTH(1-84) and the Sigma synthetic PTH elute as a peak showing a symmetrical profile. *See* ¶ 18 of Declaration 2. However, an analytical gel electrophoresis with material from the two peaks after the second HPLC, carried out via silver staining of an SDS-PAGE gel, showed that the Sigma synthetic PTH preparation contained a significant high molecular weight impurity, in addition to low weight impurities shown under the PTH band. *See* ¶ 19 of Declaration 2.

Finally, paragraphs 20-22 demonstrate that the impurities present in Sigma's synthetic PTH result in significantly reduced biological activity as compared to Applicants' claimed hPTH (1-84). This was demonstrated in an adenylate cyclase assay of recombinant hPTH(1-84) and the Sigma synthetic PTH. The relevant adenylate cyclase assay activity of the recombinant PTH(1-84) was shown to be significantly greater than that for the Sigma synthetic PTH. See ¶ 21-22 of Declaration 2.

D. Claim Rejections - 35 U.S.C. § 102

1. Rejection of Claims 38, 39, 41 and 57-59 as Being Allegedly Anticipated by Breyel et al.

Claims 38, 39, 41 and 57-59 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Breyel et al. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that the burden is on Applicants to show a novel or unobvious difference between the claimed product and the product of the prior art because the U.S. Patent and Trademark Office does not have the facilities to compare Applicants' product to the prior art product.

The cell-free medium of the claimed invention is novel and unobvious over Breyel et al. As discussed in Applicants' December 31, 2003, Amendment, the extract of Breyel et al. was obtained by lysing the cells via sonication. Because the cells of Breyel et al. were lysed, the resulting extract contains most of the soluble molecules of the cells, including proteases. The presence of such proteases during expression and purification of a recombinant protein is undesirable because such proteases would degrade the protein of interest (*i.e.*, PTH).

In contrast, the cell free medium of the claimed invention was not obtained through cell lysis. Rather, to obtain the claimed cell free medium consisting essentially of intact hPTH(1-84) molecules, the PTH is secreted into the medium by the microorganism. Because the cell free medium of the claimed invention was not obtained by lysing the cells, protein degradation of the PTH by proteases present in the cell interior does not occur.

For the reasons discussed above, the cell free medium of the present invention is not anticipated by the extract of Breyel et al. and, therefore, withdrawal of this ground for rejection is respectfully requested.

2. Rejection of Claims 38, 39, 41 and 57-59 as Being Allegedly Anticipated by Applicants' "Admission of the Prior Art"

The Examiner asserts that the specification at page 7 teaches the use of an hPTH (1-84) standard to compare and assess the results of the purification process. Further, the Examiner asserts that for the "standard" to have been useful for such comparison, it itself must have met the limitations of the pending claims.

Applicants respectfully disagree with the Examiner. However, to expedite prosecution, Applicants have amended claim 38 to recite "wherein the PTH preparation does

not contain chemically modified amino acids." As discussed above, the PTH standard, referred to on page 7 of the specification, is synthetic PTH obtained from chemical supply companies, including Peptide Institute Protein Research Foundation, Penninsula Laboratories, Sigma, and Bachem. All of the synthetic PTH preparations necessarily contain chemically modified amino acids, such as protecting groups, resulting from the chemical processes used to make the compounds.

Moreover, as described in Declaration 1, SDS-PAGE analysis of the five different synthetic PTH standards as compared to recombinant hPTH (1-84) of the claimed invention, showed that all of the five synthetic PTH compositions used as standards contained impurities. Further, as described in Declaration 2, such impurities result in decreased biological activity of the synthetic PTH and may elicit potential autoimmune reactions.

Because the synthetic PTH used by Applicants' as a PTH standard is explicitly excluded from the claimed invention, and because such PTH standards have lower biological activity as compared to Applicants' claimed hPTH(1-84), withdrawal of this ground for rejection is respectfully requested.

E. Claim Rejections - 35 U.S.C. § 103

Claims 38, 39, 41 and 57-59 are rejected under 35 U.S.C. § 103 as being allegedly obvious over Breyel et al. ("Synthesis of mature human parathyroid hormone in Escherichia coli," *Third European Congress on Biotechnology*, Vol. 3, p. 363-369 (1984)) ("Breyel") or Mayer et al. (EP 0 139 076) in view of Kaisha et al. (GB 2 092 596) ("Kaisha") and Brewer et al. (U.S. Patent No. 3,886,132) ("Brewer"). Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that although Breyel fails to disclose a hPTH that was purified from bacterial cell extracts, and Mayer fails to teach purification to the degree recited in the rejected claims, a person of ordinary skill in the art would have been motivated to purify the hPTH as taught by Breyel or Mayer using the protocol suggested by Brewer because Kaisha teaches the desirability of making large quantities of hPTH. Applicants respectfully disagree with the Examiner's analysis and conclusion.

1. The Rejection is Flawed Because the Purification Method of Breyel or Mayer Could not be Used to Purify Brewer's Biological Material

A proper rejection for obviousness under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, or device, or carry out the claimed process and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner has failed to establish a *prima facie* case of obviousness. A person of ordinary skill in the art would know that the purification procedure used to purify the hPTH of Breyel or Mayer could not be the same purification procedure used to purify the hPTH of Brewer. This is because the hPTH of Breyel and Mayer were derived from entirely different sources than the hPTH of Brewer.

Specifically, the hPTH of Brewer was purified from dried, defatted parathyroid tissue. In contrast, Breyel and Mayer disclose expression of hPTH in *E. coli* (*see* page 363, "Summary," of Breyel and page 12, line 7, of Mayer). *E. coli* has endogenous exopeptidase and endopeptidase activity which cleaves internal protease sensitive domains in PTH. *See* Mathavan et al., "High Level Production of Human Parathyroid Hormone in *Bombyx mori* Larvae and BmN Cells Using Recombinant Baculovirus," *Gene*, *167*:33-39, at 34 (1995) (Exhibit 4). Therefore, the hPTH of Breyel and Mayer contained *fragments* of hPTH. *See e.g.*, page 2, line 34, through page 3, line 8, of the present specification, where it is noted that Breyel demonstrated *E. coli* degradation of human PTH.

The cited art would not have suggested to those of ordinary skill in the art that they should, or could, purify the hPTH of Breyel or Mayer utilizing the purification procedure disclosed at col. 2, lines 3-13, of Brewer because a person of ordinary skill in the art would know that the hPTH of Breyel and Mayer contained significant amounts of hPTH fragments. A person of ordinary skill in the art would know that the hPTH of Breyel and Mayer contained significant amounts of hPTH fragments because the hPTH material was expressed

in *E. coli*. In contrast, the hPTH of Brewer did not contain hPTH fragments because it was obtained from dried, defatted parathyroid tissue.

2. One of Skill in the Art Would not Have Had a Reasonable Expectation of Success in Applying the Purification Process of Brewer to the hPTH Fragments of Breyel or Mayer

Furthermore, a person of ordinary skill in the art would not have had a reasonable expectation of success in applying the hPTH purification procedure of Brewer to the hPTH fragments of Breyel and Mayer to obtain hPTH(1-84) that meets the present claim limitations. A person of ordinary skill in the art would know that purifying hPTH(1-84) from hPTH fragments would be extremely difficult because the chromatographic properties of hPTH fragments would be similar to the chromatographic properties of intact hPTH(1-84). Therefore, a person of ordinary skill in the art would not expect the generic three step purification procedure described at col. 2, lines 3-13, of Brewer to purify the hPTH of Breyel and Mayer to yield a PTH fraction that consists essentially of intact hPTH(1-84) molecules.

At best, the Examiner is using an improper "obvious to try" standard, arguing that it would have been obvious to a person of ordinary skill in the art to try to purify the hPTH of Breyel or Mayer utilizing the purification procedure disclosed at col. 2, lines 3-13, of Brewer. However, as noted above, "'obvious to try' has long been held to not constitute obviousness." *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995).

Finally, the hPTH of Breyel is not "mature" PTH, as "mature" PTH consists only of the known 84 amino acids of PTH, and does not additionally include other fused amino acid residues. *See e.g.,* Mahoney (WO 84/01173) at page 12, lines 1-2 and 33-37; and page 13, lines 27-32, referring to a "mature" protein (Exhibit 5).

For at least the foregoing reasons, the cited prior art does not teach or suggest the claimed invention and, therefore, withdrawal of this ground for rejection is respectfully requested.

Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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